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Original article

Association of public health and social measures on the hand-foot-mouth epidemic in South Korea

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ABSTRACT

Background: School based-measures such as school closure and school holidays have been considered a viable intervention during the hand-foot-mouth disease (HFMD) epidemic. The aim of this study was to explore the association of nationwide public health and social measures (PHSMs) including planned school vacation on the transmissibility and attack rate of the HFMD epidemic in South Korea.
Methods: In this study, we used Korean national surveillance data on HFMD from 2014 to 2019 to estimate the temporal changes in HFMD transmissibility (instantaneous reproductive number, R_t). Furthermore, to assess the changes in the HFMD attack rate, we used a stochastic transmission model to simulate the HFMD epidemic with no school vacation and nationwide PHSMs in 2015 South Korea.
Results: We found that school vacations and 2015 PHSMs were associated with the reduced R_t by 2–7 % and 13 %, respectively. Model projections indicated school vacations and 2015 PHSMs were associated with reduced HFMD attack rate by an average of 1.10 % (range: 0.38–1.51 %).
Conclusions: PHSMs likely have a larger association with reduced HFMD transmissibility than school-based measures alone (i.e. school vacations). Preventive measures targeting preschoolers could be considered as potential options for reducing the future burden of HFMD.

Introduction

Hand-foot-mouth disease (HFMD) is a communicable disease that primarily affects children and is characterized by rashes or vesicular appearance on the hands, feet, and tongue [1]. HFMD is caused by RNA viruses belonging to the Picornaviridae family, such as enteroviruses and coxsackieviruses, and is spread through direct contact with contaminated saliva or fomites [2]. While the number of mild cases of HFMD vastly outnumbers severe cases, HFMD is a high-incidence pediatric disease that affects millions of children every year across Asia, and is estimated to cause 97,000 disability-adjusted life-year losses per annum [3]. The HFMD is usually self-limiting. However, it can result in complications associated with the central nervous system [1,3], and neurological symptoms including seizure and lethargy are known to be associated with increased mortality in patients with HFMD [4].

HFMD epidemics recur in South Korea from April to August, peaking in late June or July each year, and their annual socio-economic burden is estimated to be approximately 100 million USD [5]. Several studies have demonstrated that meteorological factors such as temperature, rainy season, and humidity may affect the seasonality of HFMD [6,7], and HFMD epidemics have been linked to school activity in kindergartens and childcare centers [8,9]. Therefore, school closures may be a viable intervention during an HFMD epidemic [2,10]. However, the effectiveness of school-based interventions such as scheduled school holidays (i.e., school vacation) or reactive school closures in reducing the HFMD burden is

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controversial [9,11]. Furthermore, as public health and social measures (PHSMs) are rarely used to mitigate HFMD transmission, the evidence demonstrating the benefits of nationwide PHSMs in the community setting remains limited at present [9].

In South Korea, the summer school vacation is typically for a month between mid-July and mid-August [7]. The school vacations from 2014 to 2019 and the nationwide PHSMs for the epidemic of Middle East respiratory syndrome coronavirus (MERS-CoV) in 2015 coincided with the HFMD season, allowing us to assess their association on the HFMD epidemic.

Thus, this study aimed to quantify the relation of planned school holidays and nationwide PHSMs in 2015 on the HFMD epidemic in South Korea.

Methods

Study design

This was a retrospective observational study based on the HFMD nationwide surveillance data between 1 January 2014 and 31 December 2019 in South Korea. South Korea, a country in East Asia located on the southern half of the Korean peninsula, has 51.7 million people and four distinct seasons.

Data sources and description

We obtained case-based weekly sentinel surveillance of HFMD data during 1 January 2014 through 31 December 2019 from the Korea Disease Control and Prevention Agency (KCDA) [12]. This nationwide surveillance was carried out through a network of 100 pediatric clinics, which reported all cases of HFMD, including probable and confirmed cases, and the total number of patients seen, to the KCDA. We estimated the weekly number of patients with HFMD in South Korea by accounting for the overall number of patient visits in pediatric clinics obtained from the Korean national health insurance service (which covers 95 % of the Korean population) [13]. The clinical criteria for a notified case of HFMD were the individuals with symptoms: rashes and/or vesicles on hands, feet, and tongue [14]. Along with the numbers of patients with HFMD, the weekly confirmed cases of MERS-CoV were collected from the KCDA's National Notifiable Infectious Diseases database [12]. The period of PHSMs implementation for MERS-CoV in 2015 was defined based on the press release from public health authorities (Supplementary). From the South Korean Meteorological Administration, we retrieved the data for the timing and rain gauge (cm) of the rainy season (i.e., the monsoon), which was the period with heavy rains in the Korean peninsula, for 2014–2019 [15]. We also retrieved daily relative humidity and temperature data during the study period and calculated absolute humidity, which reflects the actual amount of water vapor in the air at a given temperature (Supplementary).

Interventions and outcome variables

We considered two intervention variables accounting for the scheduled school closures (school vacations) and the PHSMs for MERS-CoV during May-July in 2015. As cases (daily/weekly) are not a real-time measure of transmission intensity, we transfer this information to a comparative unit-free metric as a measure of transmissibility. In practice, for an epidemic, the instantaneous reproduction number (R_t) is often evaluated to infer the time-varying transmissibility, which is defined as the average number of secondary cases generated by a typical primary case and R_t values < 1 indicate that the epidemic is under control [16]. In this study, we considered the outcome variables for HFMD transmission in the community by R_t along with the HFMD attack rate and compared the association of different interventions on these variables (details are below section).

Statistical analysis and modeling

To investigate the association of school vacations and 2015 PHSMs on the HFMD epidemic, we first identified the time of epidemic onset, which was chosen as the timing for which the weekly cases exceeded a pre-defined threshold of 50 % quantile of the nonzero HFMD cases during the study period [17]. We measured the epidemic duration, defined as the time between the onset and end of the epidemic, which is the retrospective ending on the same number of cases as its epidemic onset. Furthermore, we measured the epidemic peak's timing and magnitude, and the epidemic size which was defined as the total number of cases during the epidemic's duration each year. Then, we compared these measures for the year 2015 over the other years (2014 and 2016–2019) by calculating the weekly differences. In addition, we estimated the attack rate, defined as the number of cumulative cases divided by the population size. We also estimated the changes in HFMD transmissibility over time by comparing the R_t to assess the immediate association of the 2014–2019 school vacations and 2015 PHSMs on HFMD transmissibility [18].

We first used flexible cubic splines to interpolate the daily cases from weekly cases as reported in surveillance data [19,20]. We opted to utilize the branching process model to evaluate the daily R_t considering the serial interval distribution [21,22]. The serial interval, which is defined as the duration between the onset of symptoms in the primary and secondary cases, was assumed to follow a Weibull distribution, with a mean of 3.7 days and a standard deviation of 2.6 days [11]. We compared the mean R_t for two weeks before and during the interventions (school vacations and 2015 PHSMs) in each season to evaluate the mean changes in transmissibility by these interventions.

Epidemic model description and analysis

The overall association of school vacations and 2015 PHSMs on HFMD transmissibility was evaluated by fitting a multivariable regression model for R_t. This model accounted for intrinsic factors such as the initial intensity of disease transmission (i.e., basic reproduction number, R_0) and the depletion of susceptible individuals in the population at time t was represented by S_t along with other extrinsic drivers (school vacations and meteorological factors). Theoretically, the transmissibility under no interventions is given as:

$$R_t = R_0 S_t \tag{1}$$

The transmissibility of HFMD (R_t) is known to be affected by extrinsic factors such as humidity (H_t), school vacations (V_t), and 2015 PHSMs (P_t) at time t [7,11]. Therefore, we adjusted the factor of (H_t), because the incidence of HFMD in South Korea is known to increase during low rainfall (low humidity) and then decrease with increasing rainfall (or rainy season). We set H_t, a dummy variable, to indicate one for the rainy season and zero for the non-rainy season because a bivariate variable for the rainy season yielded a better-fitted regression model for R_t than a variable for absolute humidity (Table S1). V_t and P_t are indicator variables that are set to one for implementation periods and zero for non-implementation periods for vacations and 2015 PHSMs. Therefore, R_t can be expressed as [11]:

$$R_t = R_0 S_t e^{\beta_H H_t + \beta_V V_t + \beta_P P_t} \tag{2}$$

where β_H, β_V, and β_P are the parameters, indicating the effects of the rainy season, school vacations, and PHSMs, respectively (Supplementary).

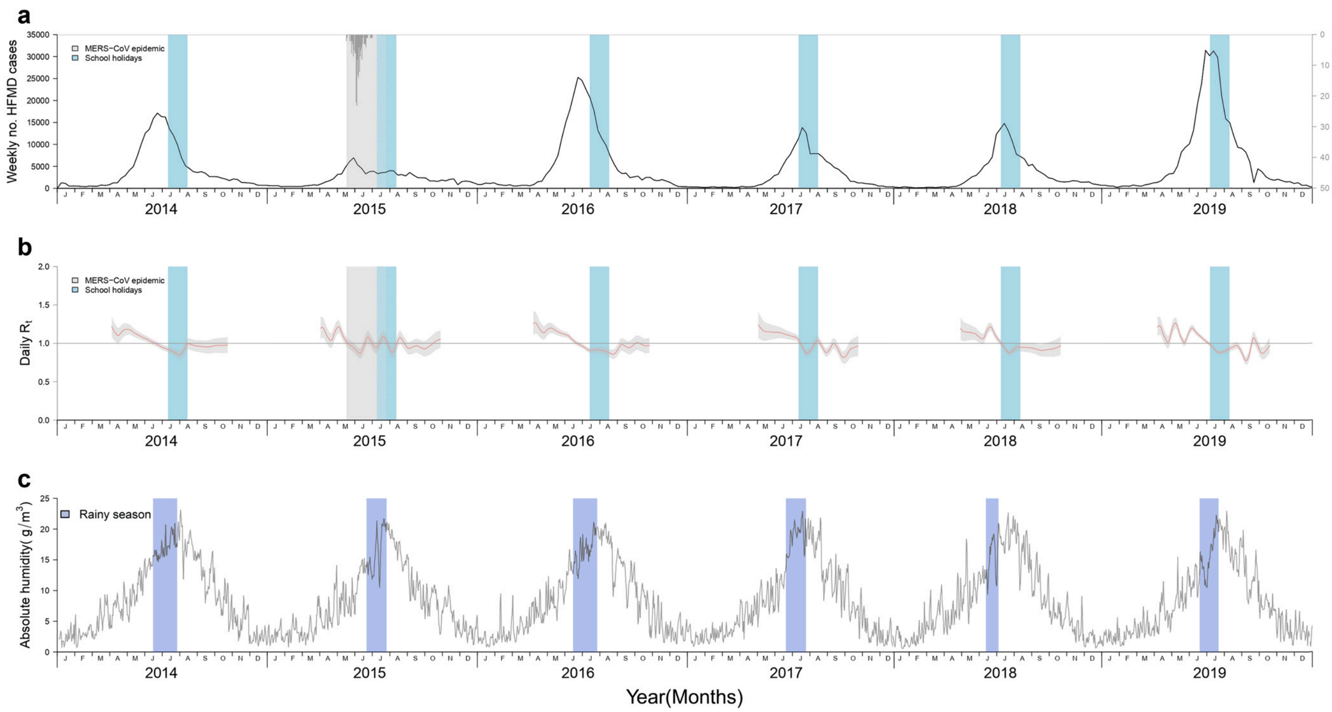

Fig. 1. Estimated HFMD activity and MERS-CoV-2 epidemic in South Korea, 2014–2019. a) The black solid line is the weekly HFMD activity, which was estimated by the HFMD consultation rate from primary clinics acquired from the Korean national surveillance system. The daily epicurve of the MERS-CoV outbreak was indicated reversely. The shaded gray bar represents the period of the MERS-CoV outbreak, and the shaded blue bar indicates the school-based measures. b) Daily effective reproductive number (R_t) of HFMD. The red solid line indicates the daily mean estimate of R_t, and the gray shaded area indicates pointwise 95 % CIs of R_t; the gray horizontal line indicates a transmission threshold (R_t= 1). c) The black solid line is the weekly absolute humidity (g/m^3) estimated from Korean Meteorological Administration. The purple horizontal bar indicates the rainy season.

To quantify the relation between PHSMs and HFMD attack rate, we simulated the HFMD incidence using a susceptible-exposed-infectious-recovered (SEIR) deterministic transmission model. The model was developed under the counterfactual scenario of with and without school vacations and non-PHSMs. Using this model, we estimated the changes in attack rate by the school vacations in 2014–2019 and the PHSMs in 2015 (Supplementary). Using the multivariable log-linear regression model (Supplementary), the regression coefficients can be estimated. We calculated the changes in overall infections by comparing the counterfactual simulated incidence/attack rate between with and without summer school vacations and PHSMs (i.e., setting β_p = 0 for the scenario without PHSMs).

All statistical analyses were performed in R version 4.0.1 (R Foundation for Statistical Computing).

Results

Fig. 1 shows the weekly number of HFMD cases, estimated daily R_t, and absolute humidity and the rainy season during the study period.

The epidemic onset and peak timing for the HFMD epidemic in 2015 were identified on average 1.74 (range: 0.6–3.0) weeks leading and 6.6 (range: 3.9–8.2) weeks leading, respectively, in comparison with other usual years (2014 and 2016–2019) (Table 1). The average peak magnitude and attack rate for the 2015 season reduced by 1809 (range: 811–3380) cases and 1.4 (range: 0.4–3.0), respectively, while the duration of the 2015 epidemic was shortened up to 1–2 weeks comparatively.

In the two weeks prior to the school vacation during 2014–2019, the overall mean R_t was 1.01 (range: 0.93–1.08), while it dropped to 0.93 (range: 0.90–0.98) during the vacations and remained at 0.96 (range: 0.87–1.04) in the following weeks (Table 2), corresponding to an average of 7.65 % (range: 0.28–14.57 %) reduction in the R_t during the school vacations. Furthermore, the school vacations were associated with a 4.57 % (range: 1.83–6.53 %) reduction in overall HFMD transmissibility in the regression analysis for R_t adjusted for the rainy season. We also estimated that the 2015 PHSMs were associated with a 13.35 % (95 % confidence interval [CI], 9.95–16.76 %) reduction in HFMD transmissibility (Table 3).

For the association of school vacations and 2015 PHSMs on HFMD attack rate, we found that it was reduced by an average 1.10 % (range: 0.38–1.51 %) during the epidemic period (Fig. 2 and Table 4). The estimated reduction in infections was similar to that observed by sensitivity analysis for the simulation analysis with different levels of preexisting immunity (0.1–30 %) and R_0 (2.5–4.5) (Table S2 in the Supplementary).

Discussion

Changes in host susceptibility and extrinsic factors such as school holidays, PHSMs, and rainy seasons have been identified as driving factors for HFMD transmission in the community [10,11]. However, after adjustment for the rainy season, the findings of our study showed that school vacations during an HFMD epidemic season had a minor association on HFMD transmission.

School closure has been considered as one of the effective PHSMs to control epidemic and pandemic preparedness of infectious diseases in the community, because school-aged children have a higher contact rate and are more susceptible to infection than adults [23]. However, previous studies have shown that preschool children account for most cases of HFMD [24,25], implying that a school closure for HFMD alone is insufficient to restrict the infections. Another reason for the limited influence of school holidays in our study could be that the length of school vacations (around a month) was insufficient to significantly change the degree of overall transmissibility [11,26]. Our finding is comparable to the results of previous studies on influenza showing that shorter school breaks of only two

Table 1
Differences in the epidemic onset, peak timing, peak magnitude, epidemic duration, and attack rates with respect to the year 2015.

Years	Onset timing		Peak timing		Peak magnitude		Epidemic duration		Attack rates	
	Values (Week)	Δ_{2015}	Values (Week)	Δ_{2015}	Values (no. of patients)	Δ_{2015}	Values (Week)	Δ_{2015}	Values	Δ_{2015}
2014	15.1	-0.6	25.0	3.9	2257.2	1356.8	24.4	1.0	2.29	1.05
2015	15.7	-	21.1	-	900.4	-	23.4	-	1.24	-
2016	16.6	0.9	26.0	4.9	3251.8	2351.4	22.1	1.3	3.16	1.92
2017	19.6	3.0	29.1	8.1	1711.7	811.3	21.9	1.5	1.66	0.42
2018	19.6	3.0	29.3	8.2	2050.3	1149.9	21.1	2.3	1.85	0.62
2019	16.9	1.2	29.0	7.9	4281.2	3380.8	24.3	0.9	4.20	2.96

Δ_{2015}: Differences with respect to the year 2015.

Table 2
Estimated daily reproductive number R_t in South Korea during, 2 weeks before, and 2 weeks after summer school holidays in 2014–2019, and the associated reductions in R_t.

Year	Mean estimated R_t (95 % CI)			Reduction in R_t, school holidays vs. 2weeks before, % (95 % CI†)	Overall reduction in R_t associated with the school holidays, % (95 % CI†)*
	During 2 weeks before the school holidays started	During the school holidays	During 2 weeks after the school holidays ended		
2014	0.94 (0.90–0.98)	0.90 (0.84–0.95)	0.98 (0.91–1.06)	4.22 (2.54–5.9)	6.53 (5.37–7.69)
2015	0.99 (0.91–1.06)	0.98 (0.91–1.06)	1.04 (0.96–1.13)	0.28 (0.05–0.51)	1.83 (−0.58 to 4.23)
2016	0.93 (0.90–0.97)	0.91 (0.86–0.95)	0.87 (0.81–0.93)	2.75 (1.64–3.86)	2.67 (1.33–4.01)
2017	1.08 (1.03–1.12)	0.95 (0.90–1.00)	0.94 (0.89–0.99)	12.71 (12.55–12.87)	4.13 (2.25–6.01)
2018	1.07 (1.03–1.12)	0.93 (0.88–0.97)	0.95 (0.89–1.01)	14.57 (14.21–14.93)	6.01 (4.93–7.09)
2019	1.03 (1.00–1.05)	0.91 (0.88–0.94)	0.96 (0.92–1.00)	11.36 (10.87–11.84)	6.25 (3.49–9.01)

†CI: Confidence interval*Estimated from the regression model for R_t adjusted to rainy season

Table 3
Estimated daily reproductive number R_t in South Korea during, 2 weeks before, and 2 weeks after public health and social measures (PHSMs) in 2015, and the associated reduction in R_t.

Year	Mean estimated R_t (95 % CI)			Reduction in R_t, PHSMs vs. 2 weeks before, % (95 % CI†)	Overall reduction in R_t associated with PHSMs, % (95 % CI†)*
	During 2 weeks before the PHSMs were implemented	During the PHSMs	During 2 weeks after the PHSMs ended		
2015	0.99 (0.93–1.05)	0.9 (0.84–0.97)	0.99 (0.91–1.07)	8.71 (9.07–8.36)	13.35 (9.95–16.76)

†CI: Confidence interval
*Estimated from the regression model for R_t adjusted to rainy season

weeks were an effective measure for mitigating influenza transmission, which generally affects a broader range of ages [19,27].

Because many HFMD cases present with respiratory symptoms, and the patients' respiratory droplets can transmit HFMD [28], PHSMs for respiratory viruses can be considered as useful preventive measures to mitigate the HFMD epidemic. Our study showed that the 2015 PHSMs implemented for the prevention of the MERS-CoV epidemic had a significant impact on HFMD transmission. The 2015 PHSMs that were implemented at the start of the HFMD epidemic reduced the peak magnitude, and duration of the epidemic. However, in the simulation analysis for the attack rate of HFMD infections, we could not identify a significant reduction in 2015. This is likely due to the early implementation timing of the 2015 PHSMs and the low susceptible population against HFMD infection in 2015.

When compared to absolute humidity, we observed that the rainy season improved our regression model for HFMD transmissibility (Table S1 in the Supplementary). Our study also showed that the rainy season has a positive association on reduction of HFMD transmission (Table 5). This finding is similar with the findings of previous studies in which the rainy season was reported to have likely reduced outdoor activities and social mixing (i.e., rainy season offered a social-distancing benefit against the epidemic) [29,30].

As the number of MERS-CoV cases and people's anxiety grew, public mass media began to advocate for voluntary PHSMs, such as improving personal hygiene and avoiding crowds. During the MERS-CoV epidemic, the Korean ministry of education launched a student infectious disease control program on June 1, 2015, and implemented school-based measures such as frequent hand washing and sick leaves [31]. However, in accordance with the World Health Organization's recommendations, the school-based measures were relaxed on June 10, 2015, since MERS-CoV transmission was not linked to schools [32]. We found that these school-based measures had no significant impact on HFMD transmission in 2015 (associated reduction rate, 1.83 %; 95 % CI, −0.58 % to 4.28 %).

Our study had some limitations. First, we did not include viral pathogen data for HFMD because laboratory-based surveillance using small sample sizes (< 500) began in 2017. However, the available laboratory-based surveillance data suggests that coxsackievirus A16 is a major HFMD pathogen in South Korea (95 % in 2017 and 85 % in 2018; data not available for the other years) [12]. Thus, in our simulation model, it was reasonable to set the R_0 to 2.7 [33]. Furthermore, the simulated number of cases was well fit with that of observed HFMD cases during the study period (Fig. S1 in the Supplementary). Second, our results from the simulation analysis were influenced by variations in model parameters. However, in the sensitivity analysis, we found no significant difference in the levels of other parameters (Table S2 in the Supplementary). Third, we used weekly time series data, which perhaps could missed the changes within the week time (as the mean serial interval = 3.7 days), the effective delay could be identified efficiently by analysing the daily data instead, which is not in the scope of our study design. Fourth, we used syndromic data that could have been influenced by changes in healthcare-seeking behavior during the MERS-CoV epidemics. Finally, the association of these interventions with HFMD

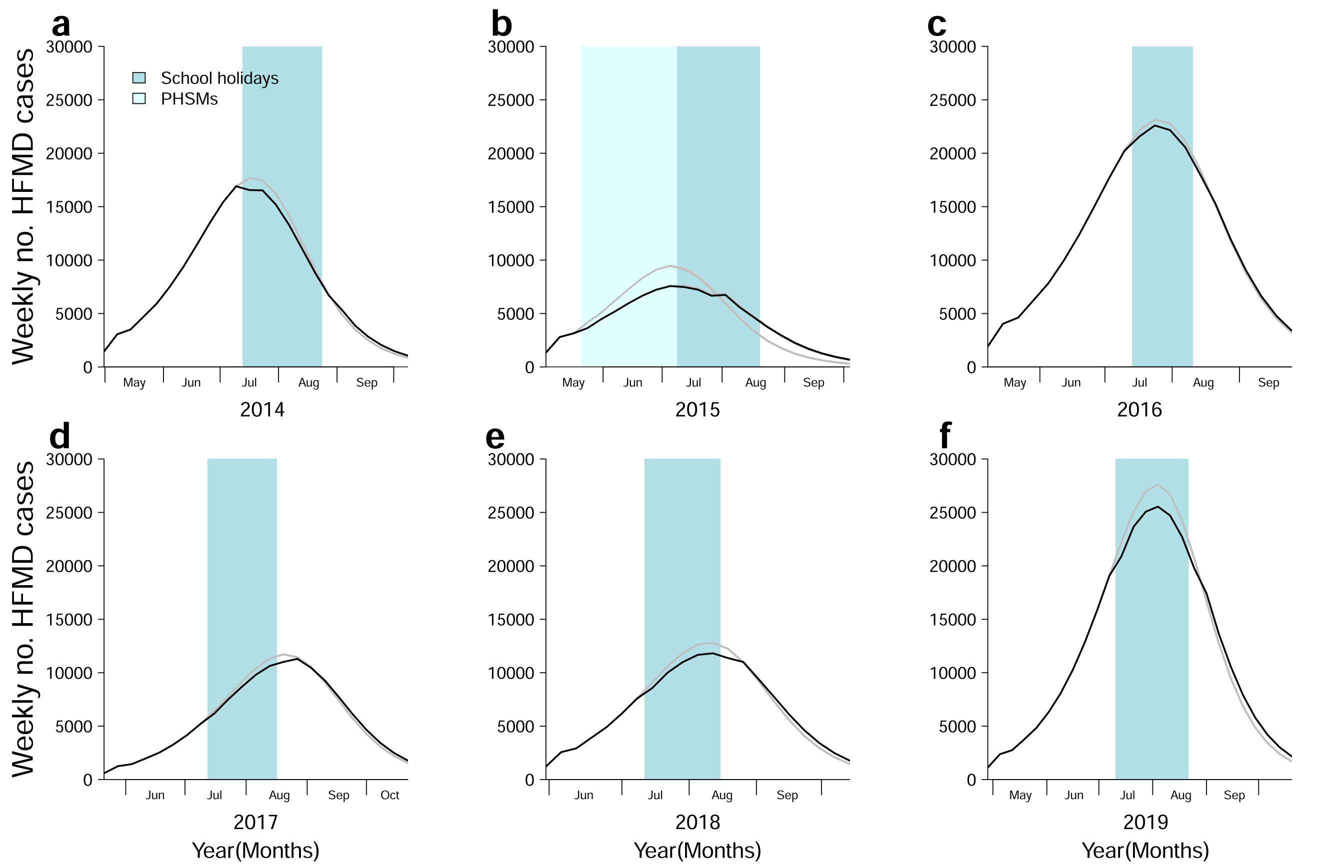

Fig. 2. Simulated incidence of HFMD with or without implementation of summer school holidays in 2014–2019 and PHSMs in 2015 in South Korea. The black solid line indicates the hypothetical scenario of the weekly HFMD incidence with summer school holidays in 2014–2019 and PHSMs in 2015 during the HFMD epidemic period. The gray line indicates the counterfactual scenario of the weekly HFMD incidence without summer school holidays in 2014–2019 and PHSMs in 2015. The difference between these two lines represents a reduction of a) 1.5 % in 2014, b) 0.5 % in 2015, c) 0.6 % in 2016, d) 0.9 % in 2017, e) 1.3 % in 2018, and f) 1.4 % in 2019.

Table 4
Differences in the cumulative incidence of hand-foot-mouth-disease (HFMD) based on simulated epidemics with and without summer school holidays and public health and social measures (PHSMs) in South Korea during 2014–2019.

Year	Cumulative incidence without summer school holidays (and PHSMs in 2015)	Cumulative incidence with summer school holidays (and PHSMs in 2015) (95 % CI†)	Reduction in cumulative incidence with school holidays (and PHSMs in 2015) (95 % CI†)	Reduction rate in cumulative incidence with school holidays (and PHSMs in 2015) (95 % CI†)
2014	200,528	197,492 (196,936–198,043)	3036 (2485–3592)	1.51 (1.24–1.79)
2015[a]	103,927	103,532 (103,005–104,051)	395 (−124 to 923)	0.38 (−0.12 to 0.89)
2015[b]	100,614	100,130 (99,484–100,766)	484 (−152 to 1130)	0.48 (−0.15 to 1.12)
2016	257,254	255,731 (254,958–256,498)	1522 (755–2296)	0.59 (0.29–0.89)
2017	132,695	131,568 (131,040–132,086)	1126 (608–1654)	0.85 (0.46–1.25)
2018	142,231	140,327 (139,974–140,677)	1903 (1553–2256)	1.34 (1.09–1.59)
2019	315,492	310,971 (308,902–312,995)	4520 (2497–6589)	1.43 (0.79–2.09)

†CI: Confidence interval
2015[a] includes only summer school holidays for the MERS-CoV-2 epidemic
2015[b] includes both summer school holidays and PHSMs for the MERS-CoV-2 epidemic

Table 5
Estimated reduction in R_t associated with the rainy season, South Korea, 2014–2019.

Year	2014	2015	2016	2017	2018	2019
Reduction in R_t, % (95 % CI†)*	5.74 (6.75–4.73)	2.79 (0.48–5.1)	4.88 (3.76–6.00)	1.34 (0.60–3.28)	6.88 (5.52–8.24)	1.00 (−1.72 to 3.72)

†CI: Confidence interval
*Estimated from the regression model for R_t adjusted to school holidays and public health and social measures in 2015

transmissibility might be affected by other causal factors as the study design was not able to disentangle all the factors, although we performed statistical and counterfactual simulation analyses to assess the impact association of these interventions.

Conclusions

In conclusion, when nationwide PHSMs were implemented, HFMD transmissibility decreased significantly, while scheduled school closure showed limited effectiveness. PHSMs targeting preschooler during the HFMD epidemic could be a potential measure for reducing the burden of HFMD.

Ethical Approval

This study was approved by the Konyang University Institutional Review Board (2022–05–003). HFMD data used in this study acquired from the publicly available surveillance report published by Korea Disease Control and Prevention Agency.

Author's contribution

SR and STA conceived the study, designed the statistical methods. SR and CH did the data collection and assimilation. SR and CH did the data analysis. SR and CH wrote the first draft of the manuscript. STA, BY and SP critically reviewed and edited the manuscript. All authors contributed to the interpretation of the results, revision of the manuscript critically and have given final approval of the version to be published.

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Data availability

The data that support the findings of this study are available from the corresponding author, SR, upon reasonable request.

Declarations of Competing Interests

The authors have no competing interests to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2023.03.029.

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